PB86-117892

Quantification of Toxicological Effects of Arsenic (Draft)

(U.S.) Environmental Protection Agency
Washington, DC

Dec 84

U.S. Department of Commerce
National Technical Information Service
NTIS.

PB86-117892

QUANTIFICATION OF TOXICOLOGICAL EFFECTS OF ARSENIC

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U. S. Environmental Protection Agency
Office of Drinking Water

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December, 1984

External Review Draft

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

FOREWORD AND ACKNOWLEDGMENT

This document is based on information regarding the health effects of arsenic contained in several reports prepared by or for the U.S. Environmental Agency. These reports are entitled "Health Assessment Document for Inorganic Arsenic-Final Report" (USEPA 1984), "Ambient Water Quality Criteria for Arsenic" (USEPA 1980), "Feasibility Study to Resolve Questions on the Relationship of Arsenic in Drinking Water to Skin Cancer" (Andelman and Barnett 1983), and "First Draft of the Drinking Water Criteria Document on Arsenic" (draft report). In some cases, portions of the texts of these documents have been abstracted for use here with only minor changes.

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1.	2.
3. RECIPIENT'S ACCESSION NO. PB86 117892/AS	
SUBTITLE: Quantification of Toxicological Effects of Arsenic	5. REPORT DATE: 12/84
	6. PERFORMING ORGANIZATION CODE
AUTHOR(S): U.S. Environmental Protection Agency	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS	10. PROGRAM ELEMENT NO.
	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS: U.S. Environmental Protection Agency, Office of Drinking Water (WH-550), 401 M St., S.W., Washington, D.C. 20460	13. TYPE OF REPORT AND PERIOD COVERED: Scientific review
	14. SPONSORING AGENCY CODE: EPA/CSD

15. SUPPLEMENTARY NOTES

16. ABSTRACT

The Criteria and Standards Division (CSD), U.S. Environmental Protection Agency has prepared a section on the toxicological effects of arsenic exposure through drinking water. This section maybe read with the Health Assessment Document for Inorganic Arsenic prepared by the Office of Health and Environmental Assessment (OHEA), U.S. EPA. This section is a review of the following topics:

- Arsenic metabolism
- Arsenic toxicology
- Arsenic mutagenicity and carcinogenicity
- Human health risk assessment for arsenic

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
Arsenic properties Arsenic toxicity		

18. DISTRIBUTION STATEMENT: OPEN	19. SECURITY CLASS (This Report): Non-sensitive	21. NO. OF PAGES
	20. SECURITY CLASS (This page): Non-sensitive	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

The quantification of toxicological effects of a chemical consists of an assessment of the non-carcinogenic and carcinogenic effects. In the quantification of non-carcinogenic effects, an Acceptable Daily Intake (ADI) is calculated. An Adjusted Acceptable Daily Intake (AADI) and Health Advisory (HA) values for the chemical are then calculated to define the appropriate drinking water concentrations to limit human exposure. For ingestion data, this approach is illustrated as follows:

$$ADI = \frac{(\text{NOAEL or LOAEL in mg/kg/day})(\text{Body Weight in kg})}{\text{Uncertainty/Safety Factor}} = \text{mg/day}$$

$$AADI = \frac{ADI}{\text{Drinking Water Volume in L/day}} = \text{mg/L}$$

where: NOAEL = no-observed-adverse-effect level.

LOAEL = lowest-observed-adverse-effect level.

Body weight = 70 kg for adult or 10 kg for child.

Drinking water volume = 2 L per day for adults or 1 L per day for children.

Uncertainty/Safety Factor = 10, 100 or 1,000.

Utilizing these equations, the following drinking water concentrations are developed for non-carcinogenic effects:

1. A one-day HA for 10-kg child
2. A one-day HA for 70-kg adult

3. A ten-day HA for 10-kg child
4. A ten-day HA for 70-kg adult
5. A lifetime AADI for a 70-kg adult.

The distinctions made between the HA calculations (items 1 through 4) are associated with the duration of anticipated exposure. Items 1 and 2 assume a single acute exposure to the chemical. Items 3 and 4 assume a limited period of exposure (possibly 1 to 2 weeks). The HA values will not be used in establishing a drinking water standard for the chemical. Rather, they will be used as informal scientific guidance to municipalities and other organizations when emergency spills or contamination situations occur. The ADI value (item 5) is intended to provide the scientific basis for establishing a drinking water standard based upon non-carcinogenic effects.

A NOAEL or LOAEL is determined from animal toxicity data or human effects data. For animal data, this level is divided by an uncertainty factor because there is no universally acceptable quantitative method to extrapolate from animals to humans. The possibility must be considered that humans are more sensitive to the toxic effects of chemicals than are animals. For human data, an uncertainty factor is also used to account for the heterogeneity for the human population in which persons exhibit differing sensitivity to toxic chemicals. An Office of Drinking Water (ODW) modification of the guidelines set forth by the National Academy of Sciences (NAS 1977,

1980) is typically used in establishing uncertainty factors as follows:

- An uncertainty factor of 10 is used when good acute or chronic human exposure data are available and are supported by acute or chronic toxicity data in other species.
- An uncertainty factor of 100 is used either when good acute or chronic toxicity data identifying a NOEL/NOAEL are available for one or more species (but human data are not available), or when good acute or chronic toxicity data identifying a LOAEL in humans are available.
- An uncertainty factor of 1,000 is used either when limited or incomplete acute or chronic toxicity data are available, or when only the acute or chronic toxicity data identify a LOAEL (but not a NOEL/NOAEL) for one or more species.

The uncertainty factor used for a specific risk assessment is judgmental. Factors that cannot be incorporated in the NAS/ODW guidelines for selection of an uncertainty factor, but must be considered include: (1) the quality of the toxicology data, (2) the significance of the adverse effects and (3) the existence of counterbalancing beneficial effects.

If toxicological evidence requires the chemical to be classified as a potential carcinogen (there is sufficient evidence to classify arsenic as a carcinogen in humans

following ingestion), mathematical models are used to calculate the estimated excess cancer risks associated with the ingestion of the chemical via drinking water. The bioassay data used in these estimates are from animal experiments. In order to predict the risk for humans, these data must be converted to an equivalent human dose. This conversion includes correction for non-continuous animal feeding, non-lifetime studies and for the difference in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average human body weight is 70 kg and that the average human consumes 2 liters of water per day. The multi-stage model is then fit to the equivalent human data to estimate the risk at low doses. The upper 95 percent confidence limit of this estimate is used. Excess cancer risks can also be estimated using other models such as the one-hit model, the Weibull model, the logit model and the probit model. There is no basis in the current understanding of the biological mechanisms involved in cancer to choose among these models. The estimates of low doses for these models can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of risk rate levels has an inherent uncertainty. This is because the tools of scientific measurement, by their very nature, involve both systematic and random error. In most cases, only studies using experimental animals have been

performed. There is thus uncertainty when the data are extrapolated to humans. When developing risk rate levels, several other areas of uncertainty exist, such as (1) incomplete knowledge concerning the health effects of contaminants in drinking water, (2) the impact of test animal age, sex and species and the nature of target organ systems examined on the toxicity study results and (3) the actual rate of exposure of internal targets in test animals or humans. Dose-response data are usually only available for high levels of exposure, not for the lower levels of exposure for which a standard is being set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

A. Non-Carcinogenic Effects

Arsenic is a metalloid element (atomic number 33, atomic weight 74.9) in Group V of the periodic table. Arsenic occurs naturally most often in sulfidic ores along with other metals (e.g., copper, nickel and cobalt), and smelting of these ores generates arsenic trioxide (As_2O_3). This compound is slightly soluble in water, forming arsenous acid (H_3AsO_3). Arsenic pentoxide (As_2O_5), formed by oxidation of As_2O_3, is readily soluble in water, forming arsenic acid (H_3AsO_4). Both arsenous (As^{+3}) and arsenic (As^{+5}) acids form salts with alkali metal ions, the solubility of the salt depending on the cation. In aerated water, As^{+3} tends to be oxidized to As^{+5}, especially

at alkaline pH. Reduction of As^{+5} to As^{+3} may occur at low pH (Buchet et al. 1980, Feldman 1979).

Soluble inorganic arsenic salts are well absorbed (70% to 95%) from the gastrointestinal tract (Coulson et al. 1935, Bettley and O'Shea 1975). Insoluble arsenic compounds (e.g., As_2Se_3) are poorly absorbed (Mappes 1977). Absorbed arsenic distributes throughout the body, and tends to accumulate with time in nails, hair, bone and skin (Kadowaki 1960). In humans and other mammals, arsenic is metabolized to form monomethyl arsenic acid (MMAA) and dimethyl arsenic acid (DMAA) (Braman and Foreback 1973, Crecelius 1977). Reduction of As^{+5} to As^{+3} has been demonstrated in animals (Rowland and Davies 1982, Vahter and Envall 1983), but has not been well documented in humans. Arsenic is excreted primarily via the urine, initially in the same form as the ingested arsenic, and later as MMAA and DMAA (Crecelius 1977). The rate of renal clearance depends somewhat on valence (As^{+5} or As^{+3}) and dose. Typically, 50% to 90% of a dose is cleared within two to four days (Crecelius 1977, Braman and Foreback 1973), primarily as MMAA and DMAA. In contrast to this relatively rapid clearance in humans, arsenic is retained in the red blood cells of rats with a half-time of 60 to 90 days (Lanz et al. 1950). For this reason, the rat is not an appropriate model for assessing arsenic toxicity in humans.

1. Short-Term Exposure

The toxicity of arsenicals depends on a number of factors, including the chemical and physical form of the compound, the route of exposure, the dose and duration of exposure, dietary levels of interacting elements and the age and sex of the exposed subjects.

Oral LD_{50} values for As_2O_3 range from 15 to 293 mg/kg in rats and from 26 to 43 mg/kg in mice (Dieke and Richter 1946, Harrison et al. 1958, Done and Peart 1971). In general, arsenites (As^{+3}) are several times more toxic than arsenates (As^{+5}), and soluble compounds are more toxic then insoluble compounds. In humans, ingestion of an acute lethal dose or arsenic produces throat constriction, difficulty in swallowing, intense thirst, epigastric distress with vomiting and diarrhea, cramps in the arms and legs, a severe fall of blood pressure, restlessness, convulsions and death due to cardiac failure (Driesback 1980). The estimated lethal dose in humans is 70 to 180 mg (1.0 to 2.6 mg/kg for a 70-kg adult) (Vallee et al. 1960).

Acute arsenic poisoning in domestic and farm animals is common. In an evaluation of records from 13 North American Veterinary colleges between 1964 and 1974, Selby et al. (1977) found descriptions of arsenic poisoning in cats, dogs, horses, pigs and cattle. Signs of acute poisoning included intense

abdominal pains, staggering, weakness, trembling, gastrointestinal actions, salivation, vomiting, diarrhea, fast feeble pulse, prostration, hypothermia, collapse and death. No quantitative data on exposure levels were reported.

Heywood and Sortwell (1979) studied arsenic intoxication in the rhesus monkey. Three pairs of adolescent monkeys (2 to 2.5 years, 3.0 to 3.25 kg) were dosed with 0, 2.8 or 5.7 mg As^{+5}/kg/day (given as As_2O_3 in milk). Both animals receiving the high dose displayed loss of condition, vomiting and diarrhea within five days, and were sacrificed on day 13 for humane reasons. Histological examination of tissues showed vacuolation of hepatocytes and dilation of proximal renal tubules. One animal receiving the low dose (2.8 mg As^{+5}/kg/day) developed an unnatural posture in one arm, but no other clinical, pathological or morphological changes were observed. This suggests that a dose of 2.8 mg/kg/day is a LOAEL, perhaps close to the NOAEL, in adolescent monkeys, although too few animals were employed to permit a strong conclusion.

Woods and Fowler (1978) investigated the effects of arsenate exposure on heme biosynthesis in mice. Male C57 Black mice (20 to 30 g) were divided into four groups of 12 animals and were supplied with drinking water containing 0, 20, 40 or 85 ppm arsenic (as sodium arsenate). The authors stated this was equivalent to doses of 0, 6.6, 11.4 or 25.1 mg/kg/day. Animals receiving the highest dose (85 ppm) experienced a 10%

weight loss, but no other external changes in weight, behavior or appearance were noted. After exposure for up to six weeks, animals were sacrificed and the activities of four hepatic enzymes involved in heme biosynthesis were measured. The first enzyme in the pathway (ALA synthetase) was depressed 17% ($P < 0.05$) at 40 ppm, but not at 20 or 85 ppm. No effect was seen on ALA dehydratase, while Uro I synthetase was increased 10% to 34% ($P < 0.05$) at all doses. The final enzyme in the pathway (heme synthetase) was decreased by 10% to 25% at all doses ($P < 0.05$). Concomitantly, urinary uroporphyrin and coproporphyrin levels were increased (142% to 910% of control) at doses of 40 and 85 ppm ($P < 0.05$), but were not significantly increased at 20 ppm. Assuming that the small changes in enzyme levels seen at the low dose (which are not accompanied by altered urinary porphyrin excretion) do not constitute an adverse effect, this study identifies the 20 ppm dose (6.6 mg/kg/day) as a NOAEL in mice exposed for six weeks.

A number of studies in animals indicate that arsenic is teratogenic. Most studies have involved parenteral administration of arsenite (Ferm et al. 1971, Ferm and Carpenter 1968, Holmberg and Ferm 1969, Beaudoin 1974), but oral exposure also has fetotoxic or teratogenic consequences. Hood et al. (1977) found that single oral doses of sodium arsenate (120 mg $NaAsO_2$/kg, 43 mg As/kg) administered by gavage to pregnant Swiss-Webster mice on day 9 or 10 of gestation resulted in 17% to 26% dead or resorbed fetuses, a 10% to 16% decrease in average

fetal weight, and a 1% to 3% rate of grossly malformed fetuses. These effects were less severe than the effects produced by intraperitoneal doses of 40 mg $NaAsO_2$/kg (14 mg As/kg). Similar results were obtained by Hood et al. (1978). Single oral doses of sodium arsenate (43 mg As/kg) given on day 11 of gestation resulted in decreased average fetal weight ($P < 0.01$), but no statistically significant incidence of gross malformations in live fetuses. As before, an intraperitoneal dose of 14 mg As/kg was more fetotoxic and teratogenic than the oral dose of 43 mg As/kg.

A large number of studies have documented the acute effects of arsenic poisoning in humans. Signs and symptoms which have been reported include peripheral neuropathy (Jenkins 1960, Chhuttani et al. 1967, Le Quesne and McLeod 1977), anemia, leukopenia, neutropenia and eosenophilia (Kyle and Pease 1965, Westhoff et al. 1975, Lerman et al. 1980), renal necrosis (Gerhardt et al. 1978) and effects on the heart (Glazener et al. 1968, Goldsmith and From 1980).

Unfortunately, accurate exposure information is rarely available in human studies, and only a few reports provide data which are useful for estimating a NOAEL or LOAEL. One source of information is the older clinical literature regarding the medicinal use of Fowler's solution (As_2O_3 dissolved in potassium bicarbonate). As described by Holland (1904), a patient was typically given five drops (about 9 mg of arsenic

trioxide, or 6.8 mg of arsenic), well diluted, after meals (i.e., three times a day). This corresponds to a dose of 0.29 mg/kg/day, assuming a body weight of 70 kg. The dose was increased one drop daily until the disease was under control or until the eyelids puffed and the bowels moved too freely. The dose was then reduced to a safer quantity, and continued until the warning returned, when it was again reduced. For some persons, even the minimum dose produced unpleasant effects; one case of erythroderma was reported after a patient received 10 mg of arsenic trioxide (7.6 mg of arsenic) taken over a two-day period. This corresponds to a dose of only 0.05 mg/kg/day.

Mizuta et al. (1956) reported that signs of peripheral neuropathy were present in 20% of a group of 220 patients who had ingested contaminated soy sauce for a period of two to three weeks. It was estimated that daily intake was about 3 mg As (probably as calcium arsenate). This corresponds to a dose of 0.05 mg/kg/day in a 60-kg Japanese adult.

Severe CNS defecits were observed in children exposed for several months as infants to arsenic-contaminated powdered milk (Hamamoto 1955, Okamura et al. 1956).

A summary of the studies regarding short-term arsenic toxicity is presented in Table VIII-1.

Table VIII-1 Summary of Studies on Short-Term Arsenic Toxicity

Reference	Species	Exposure route	Duration	Dose (mg As/ kg/day)	Result
Hood et al. (1977, 1978)	Mouse	Gavage	Day 9, 10 or 11 of gestation	43	Fetotoxicity
Heywood and Sortwell (1979)	Monkey	Oral (milk)	13 days	2.8	LOAEL
				5.7	Severe adverse effects
Woods and Fowler (1978)	Mouse	Oral (water)	6 weeks	6.6	NOAEL
				11.4	LOAEL (altered heme biosynthesis
				25.1	Decreased weight
Holland (1904)	Human	Oral (Fowler's solution)	?	0.29	NOAEL in most
			2 days	0.05	LOAEL in a few
Mizuta et al. (1956)	Human	Oral (Soy sauce)	2-3 weeks	0.05	Peripheral neuropathy
Hamamoto (1955)	Human	[Data to be Added]			
Okamura et al. (1956)	Human	[Data to be Added]			

2. Long-Term Exposure

Chronic exposure of animals to arsenic results in effects which are generally similar to those seen following acute exposure. Tissues which are effected adversely include the gastrointestinal, cardiovascular, hematopoietic, renal, nervous and respiratory systems.

Byron et al. (1967) investigated the pathological changes produced in dogs by chronic feeding of sodium arsenate or sodium arsenite. Forty-eight beagle dogs, approximately six months old, were divided into eight groups of six, and fed either Na_2HAsO_4 or $NaAsO_2$ at levels of 5, 25, 50 or 125 ppm in the diet. Two groups of six animals served as controls. Assuming an average body weight of 12 kg, and consumption of 0.5 kg food/day (Arrington 1972), this corresponds to average daily doses of 0.2, 1.0, 2.1 or 5.2 mg As/kg/day. Four of the six animals fed the high dose (125 ppm) of arsenite died within nine months. Another was found moribund and sacrificed at eight months, and the last animal died after 19 months. Anorexia and listlessness were the chief external manifastations, with weight losses of 44% to 61% of starting values. Hematologic examination revealed a slight to moderate anemia, and microscopic changes observed were those of inanition (atrophy of numerous tissues). One animal fed 50 ppm arsenite and one control animal died during the two-year period, both showing pronounced weight loss. No external differences were

noted between the surviving arsenite-exposed animals and the controls, and no noteworthy internal changes were observed at necropsy. Only one of the animals in the group fed 125 ppm arsenate died of causes related to arsenic, although weight depression and mild anemia were noted. The authors concluded that dogs consuming 50 ppm of either As^{+3} or As^{+5} did not differ from controls. On this basis, a chronic NOAEL of 2.1 mg As/kg/day is identified in dogs.

Heywood and Sortwell (1979) studied the effects of arsenic (As_2O_3) fed in milk to rhesus monkeys for a period of one year. Four test groups were employed: Group 1 consisted of three animals dosed with 2.8 mg As/kg/day, beginning on the third day of life; Group 2 consisted of four animals dosed with 2.8 mg As/kg/day, beginning in the eighth week of life; Group 3 consisted of four animals dosed with 5.7 mg As/kg/day, beginning in the eighth week of life; Group 4 consisted of two animals not dosed with arsenic (control). One out of the animals in each of Group 1 and Group 2, and three of the animals from Group 3 died during the experiment. Symptoms came on suddenly, and death occurred within 24 hours of the onset of the symptoms. Sudden weakness, dehydration along with bronchopneumonia, hemorrhage, edema and necrosis in the brain were seen in Group 1. In Group 3, acute inflammation of the small intestine and moderate regression of the thymus were seen. The animals which survived had normal levels of neurological function. EEGs were normal, and no ophthalma-

scopic abnormalities were present. Two surviving animals from Group 2 were observed for 52 weeks following the 52-week exposure. No evidence of delayed toxicity was detected. This experiment indicates that a dose of 2.8 mg As/kg/day may be fatal in some individuals, while having little effect in others. A dose of 5.7 mg As/kg/day produced death in 3/4 animals.

Schroeder and Balassa (1967) studied the effects of arsenic on growth and survival in Charles River CD mice. Animals were born and raised in a special environment and fed a special diet, all designed to minimize exposure to trace metals. At weaning, 54 males and 54 females were given water containing 5 mg As/L (as $NaAsO_2$), equivalent to an average dose of 0.35 mg/kg/day, assuming daily consumption of 70 mL water/kg body weight (Schroeder and Balassa 1967). A group of 54 males and 54 females served as controls. Growth rates and body weights were not affected after 180 days exposure, but there was a decrease in body weight apparent in male mice at 360 days ($P < 0.05$) and at 540 days ($P < 0.005$). There was a decrease in survival rates at 18 months in males ($P < 0.025$) and at 21 months in females ($P < 0.05$). Median life span was reduced by 74 and 76 days in males and females, respectively. This study identifies a dose of 0.35 mg/kg/day as a LOAEL in mice.

Schroeder and Mitchener (1971) studied the effect of

arsenic on reproduction in three generations of Charles River mice (19 litters, F_1; 25 litters, F_2; 7 litters, F_3) receiving 5 ppm arsenite in distilled water. This corresponds to a dose of about 0.35 mg/kg/day, assuming daily consumption of 70 mL water/kg body weight (Schroeder and Balassa 1967). Mice exposed to arsenic survived well through the third generation. There were no runts in 494 progeny, eight young deaths, one failure to breed and no maternal deaths. The only abnormal effects noted were a change in the ratio of males to females (from 1.03 to 1.30 in the F_2 generation, and from 1.00 to 1.71 in the F_3 generation) and a decrease in average litter size in all three generations ($P < 0.05$). This study indicates a dose of 0.35 mg/kg/day is a LOAEL in mice.

In humans, chronic arsenic poisoning is often insidious in onset, with symptoms which may attend a variety of other disorders. Early signs include weakness, languor, anorexia, nausea and vomiting, with diarrhea or constipation. As poisoning progresses, symptoms become more characteristic and include diarrhea, edema (especially of the eyelids and ankles), skin pigmentation and hyperkatosis. At later stages, signs of hepatic, renal, erythropoietic and nervous system involvement become evident (Harvey 1970).

Most studies of chronic arsenic exposure in humans have focused on the dermal disorders which occur. Because these lesions are considered to be pre-cancerous and may develop

into skin cancer, these studies are discussed in Section VIII.C (Carcinogenicity).

Only a few studies provide dose-response data regarding non-carcinogenic effects following chronic arsenic exposure in humans. Silver and Wainman (1952) described a patient who ingested 4.4 to 8.8 mg of arsenic trioxide (3.3 to 6.7 mg As) as Fowler's solution daily for a total period of 28 months, as a remedy for asthma. This corresponds to an average dose of about 0.05 to 0.1 mg As/kg/day, assuming a body weight of 70 kg. Signs of arsenic poisoning, manifested as increased freckling and as darkening of the nipples, first appeared in association with gastro-intestinal symptoms after 13 months. Redness and puffiness about the eyes and hyperkeratoses developed at approximately 18 months. Neurologic symptoms in the form of paresthesia and weakness were the last to be noted, occurring after two years. When arsenic intake was stopped, the pigmentation lightened, but the hyperkeratoses remained, and the asthma became more difficult to control.

Espinoza (1963) studied the incidence of arsenic poisoning in Torreon, Mexico, where a population of 496 people used well water containing 4 to 6 ppm (4 to 6 mg/L) of arsenic for a period of nine years. Of the 496 people, 297 (60%) showed mild signs of arsenic poisoning, 70 (14%) showed severe signs, 8 (1.6%) showed very serious symptoms, and 2 died. This study indicates that water concentrations of 4 to 6 mg/L (4000 to

6000 ug/L) produce arsenic poisoning in over half of an exposed population. Assuming a 70-kg adult consumes 2 L/day, this corresponds to a dose of 0.11 to 0.17 mg/kg/day.

Zaldivar (1974) reported on the incidence of chronic arsenic poisoning in the population of Antofagasta, Chile, before and after installation of a water treatment plant. Arsenic poisoning was diagnosed on the basis of the following symptoms: weight loss, diarrhea, debility, anorexia, scaling of the skin, hyperkeratoses, leukodermia, melanodermia, bronchitis and Raynaud's disease (often with pain).

Before operation of the plant, the average arsenic concentration in water samples was 0.58 mg/L. In a subsequent report (Zaldivar and Guillier 1977), it was estimated that average doses of arsenic were about 0.14 mg/kg/day in infants (age 0 to 5 months), about 0.06 mg/kg/day in children up to ten years old, and about 0.02 mg/kg/day in children 11 to 20 years old. Assuming consumption of 2.8 liters of water per day by an adult (Zaldivar and Guillier 1977), the average dose in adults would also be about 0.02 mg/kg/day.

During this time period, the incidence of chronic arsenic poisoning was 146/100,000 in males and 168/100,000 in females. Of these cases, a majority (51%) occurred in children (age 0 to 10 years), with progressively fewer cases in each older age bracket. The author indicated that this could be due to

higher exposure levels in children (due to higher water consumption per unit body weight), or to higher frequency of medical attention being sought for children than for adults.

After the water treatment plant began operation, the average arsenic concentration in treated water decreased to 0.08 mg/L, and the incidence of chronic arsenic poisoning fell to 9/100,000 in males and 10/100,000 in females. This study indicates that a water concentration of 0.58 mg As/L (580 ug/L) produces a significant incidence (about 0.15%) of adverse effects in a human population, especially children. This incidence is dramatically reduced (to a frequency of about 0.01%) by reduction of the arsenic content of the water to 0.08 mg/L (80 ug/L). Zaldivar and Guillier (1977) noted that the great majority of the children with chronic arsenic poisoning were from a low socio-economic environment, and indicated that it was probable that low nutritional status favored the chronic toxic effects of arsenic.

Tay and Seah (1975) described 74 cases of arsenic exposure in Singapore, where the use of arsenic-containing anti-asthmatic herbal preparations was common. The symptoms observed were typical of arsenic poisoning, with involvement of the cutaneous (92%), neurological (51%), gastrointestinal (23%), hematological (23%) and renal (14%) systems. In addition, four patients (5%) developed internal malignancies. The precise exposures could not be determined, but nearly 40% of

the patients had taken the medicine for less than six months. Other exposures ranged from 1 to 15 years. Assuming patients ingested the pills according to the recommended dosage, daily intake was calculated to be about 10.3 mg As/day for the one formulation producing the most cases of acute and chronic poisoning. Estimated intake from another formulation was 3.3 mg As/day. Although there is considerable uncertainty in these exposure estimates, the results suggest that doses of 3 to 10 mg As/day (0.05 to 0.17 mg/kg/day in a 60-kg Chinese adult) produce significant adverse effects within six months.

A summary of these studies of the long-term toxicity of arsenic is presented in Table VIII-2.

3. Beneficial Effects

Early studies to determine if arsenic is a required nutrient in animals were inconclusive (NAS 1977, Underwood 1977). More recently, several carefully controlled studies have provided evidence for nutritional beneficiality for arsenic in at least some mammalian species.

Schwartz (1977) found that 16 rats fed diets with less than 0.05 ppm sodium arsenite failed to gain weight, while rats that received 0.5, 0.75, 1 or 2 ppm (12 to 17 animals per group) experienced 15% to 23% weight gains. Arsenite was more effective than other arsenate compounds tested.

Table VIII-2 Summary of Studies on Long-Term Arsenic Toxicity

Reference	Species	Exposure route	Duration	Dose (mg As/ kg/day)	Result
Byron et al. (1967)	Dog	Oral (food)	2 years	0.2 1.0 2.1 5.2	NOAEL (external signs, histologic examination - Death (6/6)
Heywood and Sortwell (1979)	Monkey	Oral (milk)	1 year	2.8 5.7	Death (2/7) NOAEL in others Death (3/4)
Schroeder and Balassa (1967)	Mouse	Oral (water)	2 years	0.35	LOAEL (decreased weight, decreased survival)
Schroeder and Mitchner (1971)	Mouse	Oral (water)	3 generations	0.35	LOAEL (altered ratio of male/ female, decreased litter size)
Silver and Wainman (1952)	Human	Oral (Fowler's solution)	28 months	0.05 to 0.10	LOAEL (hyperpigmentation, GI symptoms at 13 mo)
Espinoza (1963)	Human	Oral (water)	9 years	0.11 to 0.17	Signs of poisoning in over 75% of the population
Zaldivar (1974), Zaldivar and Guillier (1977)	Human	Oral (water)	Lifetime	0.14 (0-5 mo.) 0.06 (1-10 yrs) 0.02 (12 yrs - adult)	LOAEL (0.15% incidence of signs of arsenic poisoning in population, especially children)
Tay and Seah (1975)	Human	Oral (herbal medicines)	< 6 months to 15 years	0.05 to 0.17	LOAEL (various signs of arsenic poisoning)

Two brief abstracts by Nielsen et al. (1975) and Nielsen and Shuler (1978) support the suggestion that arsenic is an essential element in some species. Nielsen et al. (1975) showed that male offspring from rats that received diets with 0.03 ppm arsenic had lower growth rates than animals from mothers receiving diets with 4.0 ppm arsenate and 0.5 ppm arsenite. Arsenic deprivation also had an effect on chicks. Diets with 15 to 25 ng As/g (0.015 to 0.025 ppm) failed to support growth and development beyond four weeks, while diets with 1 ug As/g (1 ppm) did (Nielsen and Schuler 1978).

Anke et al. (1978) studied the nutritional requirements for arsenic in goats and mini-pigs fed a semi-synthetic diet containing less than 0.05 ppm arsenic. Effects attributed to arsenic deficiency were seen in both species, not only in the adult animals but in their offspring. Arsenic deficiency increased the mortality of adult goats and altered the mineral profiles for copper and manganese in the carcass. Significant reproductive effects were observed in both arsenic-deficient goats and mini-pigs, including a reduction in the normal litter size. Furthermore, the mortality of kids and piglets from the arsenic-deficient groups was significantly higher than controls. Manganese levels were elevated in arsenic-deficient kids and piglets, but no perturbations of hematological indices (hemoglobin, hematocrit or mean corpuscular concentration) were noted. This is in contrast to the experimental observations of Nielsen et al. (1975), where decreased hematocrits, elevated

iron content in spleen and increased osmotic fragility of erythrocytes were observed in arsenic deficient rats. This difference may result from the differences in arsenic metabolism in rats and other species.

Uthus et al. (1983) reported on studies with chicks that suggest that arsenic influences arginine metabolism. It was reported that arsenic deprivation influenced the effects of dietary arginine, manganese and zinc, the fluctuations of which variously affected growth, kidney arginase, plasma alkaline phosphatase, plasma urea, plasma uric acid and hematocrit. The authors suggested that the four components interacted to affect the conversion of arginine into urea and ornithine.

These studies suggest that diets containing less than 50 to 100 ppb arsenic are sub-optimal for animals. No study regarding arsenic beneficiality in humans was located, but extrapolation from the animal data suggests that 25 to 50 ug may be the daily requirement in humans (NAS 1983).

B. Quantification of Non-Carcinogenic Effects

The toxicity of arsenic appears to be influenced by the rate of its metabolism (methylation) in vivo. For this reason, studies in animals will not be considered as the basis for calculation of the HA values or the ADI, since arsenic metabolism in animals may be significantly different from arsenic

metabolism in humans. This is certainly true in the case of rats and is supported by the fact that NOAEL or LOAEL values in animals are usually higher than NOAEL or LOAEL values in humans (see Tables VIII-1 and VIII-2).

1. One-Day Health Advisory

No studies were located which provide a firm foundation for calculation of one-day Health Advisories in humans. However, the description by Holland (1904) of the clinical experience related to use of Fowler's solution indicates that a dose of 0.29 mg/kg/day is a NOAEL in nearly all people, with only a few sensitive people showing mild effects at a dose of 0.05 mg/kg/day.

Using a value of 0.29 mg/kg/day as a NOAEL, the one-day HA values for children and adults are calculated as follows:

<u>One-Day Health Advisory for Child</u>:

$$\frac{(0.29 \text{ mg/kg/day})(10 \text{ kg})}{(1 \text{ L/day})(10)(2)} = 0.14 \text{ mg/L } (140 \text{ ug/L})$$

where:

0.29 mg/kg/day = NOAEL, based on absence of early signs of arsenic toxicity in humans ingesting Fowler's solution (Holland 1904).

10 kg = assumed weight of child.

1 L/day = assumed water consumption by a 10-kg child.

10 = uncertainty factor. This factor was selected in accord with ODW/NAS guidelines for use when a NOAEL in humans is employed.

2 = additional uncertainty factor. This factor was selected because the NOAEL is based on information in adults, and children may be more sensitive to arsenic than adults.

One-Day Health Advisory in Adult:

$$\frac{(0.29 \text{ mg/kg/day})(70 \text{ kg})}{(2 \text{ L/day})(10)} = 1.0 \text{ mg/L } (1000 \text{ ug/L})$$

where:

0.29 mg/kg/day = NOAEL, based on absence of early signs of arsenic toxicity in humans ingesting Fowler's solution (Holland 1904).

70 kg = assumed weight of an adult.

2 L/day = assumed water consumption by a 70-kg adult.

10 = uncertainty factor. This factor was selected in accord with ODW/NAS guidelines for use when a NOAEL in humans is employed.

2. Ten-Day Health Advisory

INSERT TO BE ADDED.

3. Adjusted Acceptable Daily Intake

Three studies were located which provide an estimate of the LOAEL for non-carcinogenic effects of chronic arsenic exposure in humans. Silver and Wainman (1952) noted that an average daily dose of 0.05 to 0.10 mg/kg/day produced adverse effects in a single adult after 13 months. Tay and Seah (1975) found that estimated doses of 0.04 to 0.14 mg/kg/day produced adverse effects in some adults after periods of six months or longer. Zaldivar (1974) reported that water containing 0.58 mg As/L produced adverse effects in 0.15% of a population, with over half the cases occurring in children. Of these studies, the report by Zaldivar (1974) has been selected for use in calculation of the ADI, for several reasons: 1) a large population was exposed (about 138,000 residents in the city of Antofagasta); 2) reasonable dose estimates are available (Zaldivar and Guillier 1977); and 3) the report focuses on children, who appear to be at higher risk than adults. These studies (Zaldivar 1974, Zaldivar and Guillier 1977) identify an average daily dose of 0.06 mg/kg/day (60 ug/kg/day) as a LOAEL in a small fraction of exposed children (age 0 to 10 years). Using this value, the ADI is calculated as follows:

ADI:

$$\frac{(60 \text{ ug/kg/day})(10 \text{ kg})}{(20)} = 30 \text{ ug/day}$$

where:

60 ug/kg/day = LOAEL, based on signs of chronic arsenic poisoning in some children exposed to arsenic via drinking water (Zaldivar 1974)

10 kg = assumed weight of a child

20 = uncertainty factor. The basis of this factor is detailed below.

According to ODW/NAS guidelines (see page VIII-3), an uncertainty factor of 100 should normally be employed when a LOAEL in humans is used to calculate the ADI. This uncertainty factor contains a factor of 10 to account for the fact that a LOAEL (as opposed to a NOAEL) is used, and an additional factor of 10 to account for intra-human variation in sensitivity (i.e., to protect all members of the population). In this case, the LOAEL is based on the appearance of symptoms in only a small fraction of the total exposed population, and so it is presumed that these affected individuals are the most sensitive members of the population and that a factor of 2 is sufficient to account for intra-child variations in sensitivity among this group.

Using 30 ug/day as the ADI for children (the most sensitive subpopulation), and assuming consumption of one liter of water per day by a child, the AADI is calculated as follows:

AADI:

$$\frac{30 \text{ ug/day}}{1 \text{ L/day}} = 30 \text{ ug/L}$$

In support of this value, it should be noted that the data of Zaldivar (1974) showed a 15-fold decrease in the incidence of chronic arsenic poisoning (to about 0.01%) when average water concentrations of arsenic were reduced from 580 ug/L to 80 ug/L. Thus, a concentration of 30 ug As/L is expected to protect more than 99.9% of an exposed population. At this concentration, average exposure in adults would be about 60 ug/day (0.0009 mg/kg/day), assuming consumption of two liters per day by a 70-kg person. This is well below the levels of 0.05 to 0.17 mg/kg/day estimated to be the LOAEL in adults (Silver and Wainman 1952, Tay and Seah 1975). Thus, an AADI of 30 ug/L will protect both children and adults.

It should also be recalled that arsenic is beneficial in some animal species (see pages VIII-20 to 23), and the estimated beneficial intake level in humans is 25 to 50 ug/day (NAS 1983). The AADI proposed above is consistent with this estimate, yielding an average daily intake of 30 ug/day in children and 60 ug/day in adults.

C. Carcinogenic Effects

Arsenic has been found to cause chromosome abnormalities in a number of eukaryotic cell systems, both *in vitro* (Paton and Allison 1972, Zanzoni and Jung 1980, Nakamuro and Sayato 1981) and *in vivo* (Beckman et al. 1977, Burgdorf et al. 1977, Nordenson et al. 1979). Leonard and Lauwerys (1980) summarized

a number of studies on the mutagenic potential of arsenic (Table VIII-3).

One of the most characteristic effects of chronic arsenic exposure in humans is a pattern of skin disorders, beginning with hyperpigmentation and keratosis, developing in some cases into squamous cell carcinoma or basal cell carcinoma. These effects have not been consistantly produced in laboratory animals.

Sommers and McManus (1953) reported on 27 cases of multiple skin cancers. Fifteen of the patients had used Fowler's solution, seven had been treated with arsenic, two had known exposure to arsenical sprays and four had possible exposure to sprays. In three, the (presumed) means of arsenic exposure was unknown. Arsenical cancer was diagnosed on the basis of multiple keratoses of palms and soles. A variety of internal cancers (not likely to have arisen by metastisis from the skin cancers) was observed in ten (37%) of the patients. The time between arsenic exposure and development of cancer in these patients ranged from 13 to 50 years, with a mean value of 24 years. No precise estimate of exposure levels was provided, but some of the patients took Fowler's solution in "small" doses for only a few months.

Fierz (1965) examined 262 patients who had received long courses of medicinal arsenic six to 25 years previously and

Table VIII-3 Summary of Mutagenicity Tests Performed with Arsenic Compounds

Species	Compound		Test	Result
	Name	Formula		
Bacillus subtilis	Arsenic trichloride	$AsCl_3$	Rec-assay	+
	Sodium arsenite	$NaAsO_2$	Rec-assay	+
	Arsenic dimethyl-dithiocarbamate	$(CH_3)_2AsS_2CNH_2$	Rec-assay	+
	Sodium methyl arsonate	$CH_3AsNa_2O_3$	Rec-assay	-
	Calcium methyl arsonate	CH_3AsCnO_3	Rec-assay	-
Escherichia coli	Sodium arsenite	$NaAsO_2$	Reversion assay	+
	Sodium arsenate	$AsHNa_2O_4$	Reversion assay	-
	Octyl ammonium methyl arsonate	$CH_3(CH_2)_7NH_4AsCH_3O_3$	Reversion assay	-
	Dodecyl ammonium methyl arsonate	$CH_3(CH_2)_{11}NH_4AsCH_3O_3$	Reversion assay	-
Salmonella typhimurium	Methane arsonic acid	CH_3AsO_3	Reversion assay	-
	Monosodium methane arsonate	CH_4AsNaO_3	Reversion assay	-
Pennisetum typhoides	Dimethylarsinic acid	$C_2H_7AsO_2$	Pollen fertility	+
Beta vulgaris	Dimethylarsinic acid	$C_2H_7AsO_2$	Pollen fertility	-
Zea mais	p-Methyl-phenyl-arsonic acid	$CH_3C_6H_4AsO_3$	Chromosomal aberrations	+
	p-Chlorophenyl-arsonic acid	$ClC_6H_4AsO_3$	Chromosomal aberrations	+
	p-Nitrophenyl arsonic acid	$NO_2C_6H_4AsO_3$	Chromosomal aberrations	+
Allium cepa	Methyl chlorophenyl arsonic acid	$CH_3ClC_6H_3AsO_3$	Chromosomal aberrations	+
Drosophila melanogaster	Sodium arsenate	$AsHNa_2O_4$	over	

continued-

Table VIII-3 - (continued)

Species	Compound		Test	Result
	Name	Formula		
Mammals (in vitro)				
Mammalian and mouse cells	Alkyl arsonic acid	$RAsO_3H_2$	Chromosomal aberrations	+
	Dialkyl arsinic acid	$R_2AsO(OH)$	Chromosomal aberrations	+
	Alkylaminotrimethyl arsonic acid	$RNH(CH_2)_3AsO_3H_2$	Chromosomal aberrations	+
Human lymphocytes	Potassium arsenite	$KAsO_2$	Chromosomal aberrations	+
	Sodium arsenite	$NaAsO_2$	Chromosomal aberrations	+
	Sodium arsenate	$AsHNa_2O_4$	Chromosomal aberrations	+
	Diethylamine acetarsone	$C_{12}H_{21}AsN_2O_5$	Chromosomal aberrations	+
Human fibroblasts	Sodium arsenite	$NaAsO_2$	Chromosomal aberrations	+
Mammals (in vivo)				
Mouse germ cells	Sodium arsenite	$NaAsO_2$	Dominant lethals	+?
Human somatic cells	Lymphocyte tumor cells		Chromosomal aberrations	+

Adapted from Leonard and Lauwerys (1980).

found keratoses in 40% and typical skin cancer in 8%. There was evidence of a dose relationship for both keratoses and skin cancer. Patients who had received more than 400 mL of Fowler's solution (4 g of arsenic trioxide) had an incidence of hyperkeratoses of greater than 50%, but as little as 50 mL (600 mg of arsenic trioxide) had resulted in keratotic changes in one patient, and only 75 mL (750 mg of arsenic trioxide) had been consumed by one patient with skin cancer. The shortest time to cancerous change was six years, with an average of 14 years.

There have been a number of epidemiologic studies attempting to delineate the relationship between arsenic in drinking water and skin cancer. A study by Tseng et al. (1968) reported a high prevalence of skin cancer and Blackfoot disease in an area of Taiwan where drinking water was contaminated with arsenic and ergot. This study has served as the impetus for investigation in the United States.

The Taiwan study and four epidemiologic studies performed in regions of the United States containing arsenic levels above the EPA standard of 50 ug/L are reviewed below. These studies were chosen for review due to their inclusion of skin cancer as an end point in the investigations. Pertinent data are abstracted and condensed in Table VIII-4 to allow rapid comparison between study population, methods and findings.

Table VIII-4 Epidemiologic Studies Relating Skin Cancer to Arsenic in Drinking Water

Parameter	Reference: Tseng et al. (1968)	Goldsmith et al. (1972)	Morton et al. (1976)	Harrington et al. (1977)	Southwick et al. (1981)
Location	Taiwan	Lassen County, California	Lane County, Oregon	Fairbanks, Alaska	Millard County, Utah
Study population / Total population	40,421 / 103,151	98 / 171	190,871	119 / 131	145 / 223
Control population	7,500	None		113	105
Arsenic conc. in water of exposed population (mg/L)	0.01-1.82 (most values from 0.4-0.6)	Range = <0.1-1.4 Median = 0.12	Range = 0-2.15 Mean = 0.0086 (5% of all samples exceeded 0.1)	Range =0.001-2.45 Mean = 0.224	Hinckley: Range = 0.15-0.22 Mean = 0.18 Deseret: Range = 0.05-0.75 Mean = 0.21
Exposure period	Not clear (1-70 years)	No data	No data	80% exposed less than 10 years	5 years or longer
Other water constituents	High alkalinity, high levels of organics, solids, bacteria (Shen and Chen 1964), ergot alkaloids (Lu 1978).	No specific data	No data	Pb, Hg, Se levels within recommended EPA limits	Hinckley / Delta: Ba 1.2 / 0.01 Ca 3.2 / 15.4 Mg 1.8 / 6.65 Na 233 / 65 (Irgolic 1981)

continued-

Table VIII-4 - continued

Parameter	Reference				
	Tseng et al. (1968)	Goldsmith et al. (1972)	Morton et al. (1976)	Harrington et al. (1977)	Southwick et al. (1981)
Medical examinations performed	Full physical exam, with attention to skin; many skin lesions biopsied.	All health data obtained by questionnaire.	Not done; data collected from medical records (tissue pathology)	Dermatological exam; complete blood counts; peripheral nervous system examination.	Dermatological exam; blood pressure, hematocrit; neurologic tests
Results	10.6% of exposed population had "arsenical skin cancer"	No increase in arsenic-related symptoms observed	No correlation between arsenic exposure and skin cancer.	No increased incidence of skin abnormalities in exposed population; no nervous disorders; no blood disorders.	2.86% of controls and 6.25% of exposed population showed dermatological signs of arsenic. No cases of skin cancer. Some slowing of nerve conduction velocity. Increased incidence of anemia.
Relation observed between arsenic exposure and skin cancer	Dose-response	None detected	None detected	None detected	None detected

Taiwan

The study by Tseng et al. (1968) involved a study population of 40,421 individuals (21,152 female and 19,269 males) who resided in an area where drinking water had high levels of arsenic. The control group consisted of 7,500 individuals (3,192 females and 4,308 males) who lived in areas with drinking water not contaminated by arsenic. As seen in Table VIII-4, the range of arsenic concentrations in the contaminated wells was quite large, but most wells ranged from 0.4 to 0.6 mg As/L (400 to 600 ug/L). The investigators also reported a great deal of variability with time when multiple samples of drinking water from a well were analyzed. It is difficult to determine whether analyses were performed on wells which were still in use or how long they had been out of use. This fact, combined with the large variation in the concentrations found, makes it difficult to determine what the actual exposure levels were.

The original epidemiologic studies done in Taiwan did not include any measurements of arsenic in blood, urine or hair. A group of researchers from the Copenhagen University Hospital in Denmark collected samples of blood from healthy Taiwanese in Taipei and the endemic area, and from Blackfoot patients and their unaffected family members. The arsenic levels found in the plasma and red blood cells of these subjects were compared to values found in healthy controls from the Copenhagen

University Hospital (Heydorn 1970). The mean values of arsenic blood levels from this study, shown in Table VIII-5, demonstrate that the study group did have elevated blood arsenic levels.

One of the most obvious results is the large difference in arsenic levels found in the blood of Danish versus Taiwanese controls. The excessive arsenic levels in the Taiwanese controls was ascribed to higher levels of arsenic in the food and water due to geochemical differences in the two countries. The blood arsenic levels found in the Taipei controls were not significantly different from those of the healthy controls from the region of endemic arsenic related disease, so these values were pooled. It is likely that the higher arsenic levels seen in the blood of Blackfoot patients and their families is due to their consumption of water from deep wells with higher levels of arsenic contamination. The influence of the higher background arsenic levels found in the Taiwanese controls is a matter of concern when extrapolating to the U.S. population. If the high background levels reported by Heydorn (1970) truly reflect the exposure of the Taiwanese, they their background exposure is greater than that of the U.S. population.

In the surveyed Taiwan population of 40,421 individuals there were 428 cases of skin cancer. In their diagnostic criteria for skin cancer, Tseng et al. (1968) included Bowen's disease, which is a precancerous lesion. This does not change

Table VIII-5 Arsenic in Blood of Danish and Taiwanese Controls and Blackfood Disease Patients and Family Members

Sample source	Plasma		Red blood cells	
	Mean value (ng As/mL)	Number of samples	Mean value (ng As/mL)	Number of samples
Normal Danish subjects	2.4	16	2.7	7
Normal Taiwanese subjects	15.4	17	32.7	5
Blackfoot patients	32.3	33	106	5
Blackfoot family members	45.2	14	81	6

Adapted from Heydorn (1970).

the significance of their findings relating arsenic to skin cancer, since they report no disease at all in the control population. It does mean that a dose-response model derived from these data will give an over-estimate of invasive skin cancer.

In addition to the 428 cases of cancer, there were also 370 cases of Blackfoot disease. The two diseases occurred together in 61 cases, which is more often than would be expected if they were random occurrences (Tseng et al. 1968). The high fatality rate and lower median age of onset for Blackfoot disease may have led to death in individuals who otherwise would have developed skin cancer later in life. Thus, the presence of Blackfoot disease could cause an under-estimation of the risk for skin cancer from arsenic.

The etiological agent in Blackfoot disease in Taiwan may be arsenic, or arsenic combined with other agents. The quality of well water in the endemic area was extremely poor, with high levels of bacterial contamination and dissolved solids (Shen and Chen 1964). Lu (1978) reported on the presence of fluorescent compounds in the Taiwanese well water. These compounds were described as structurally similar to the ergot alkaloids lysergic acid or dihydrolysergic acid. Compounds similar to ergocalciferol (Vitamin D_2) were also found to be present in the waters. The symptoms of Blackfoot disease could also be attributed to the presence of the ergot alkaloids or

the ergolaciferol-like substances, as they are known to cause similar peripheral vascular disease (Lu 1978). The high prevalence of Blackfoot disease compared to the prevalence of peripheral vascular disease in other populations exposed to arsenic in drinking water could be due to the presence of multiple etiological agents. This is further supported by the occurrence of Blackfoot disease in individuals from villages with very low levels of arsenic in the well waters (Shen and Chen 1964), and the non-linearity of the relationship between drinking water arsenic concentration and Blackfoot disease (Lu 1978).

In summary, the study by Tseng et al. (1968) provides evidence for a causal relationship between arsenic exposure and the development of skin cancer and/or Blackfoot disease. However there are several significant limitations to this study, including the following: 1) contamination of the water with several compounds in addition to arsenic; 2) uncertainty with respect to true exposure; 3) the high "background" exposure evident in the control group; and 4) uncertainty regarding the duration of time over which the study was conducted. In addition, since the diet, economic status and mobility of the individuals in Taiwan study are so diffeent from most U.S. citizens, there is additional uncertainty whether the relationship observed in Taiwan is relevant in the United States.

Lassen County, California

Goldsmith et al. (1972) evaluated the effects of well water arsenic (0.1 to 1.4 mg/L) on the health status of residents of Lassen County, California. Complete data (questionnaire, water and hair samples) were obtained from 98 of the 171 available adults. Health data consisted of reports obtained via questionnaire on symptoms or illnesses. No particular illnesses were found to have a greater prevalence in the group exposed to elevated arsenic levels. This study contributes little to an understanding of the effects of arsenic in drinking water in the United States. No information is provided on the extent and duration of exposure. Self-reporting of symptoms on such a broad scale is unlikely to show a great deal, unless an extremely large effect is expected.

Lane County, Oregon

Morton et al. (1976) reported on a retrospective analysis of skin cancer incidence in Lane County, Oregon. The county overlies a stratum rich in arsenic known as the Fisher formation. The county was known to have high levels of arsenic in the drinking water, which resulted in sporadic cases of arsenic poisoning. Data were gathered on histologically verified cases of skin cancer from pathology files of physicians, hospitals and diagnostic services in Lane County during the years 1958 to 1971. A total of 3,691 cases of non-melanoma skin cancers

in 3,237 individuals were found. Samples of water were collected from census tracts, municipalities and some individual wells. Samples were collected over a six-year period (1968 to 1974), and mean concentrations for each census tract were determined.

Skin cancer incidence data were expressed in four sets of rates, since four denominators were available: U.S. census data from 1960 and 1970, data from a 1966 Lane County census and calculated midpoint estimates for 1963. All four sets of data were used to determine mean population estimates to obtain mean annual incidence rates for 1958 to 1971. The range of arsenic concentrations in the county water samples was quite wide (0 to 2,150 ug/L, mean = 8.6 ug/L). The squamous cell cancer incidence showed a 2:1 ratio of males to females and an overall mean annual incidence of 50 per 100,000. Basal cell cancer occurred more commonly, with a male to female ratio of 5:4 and a mean annual incidence of 88 per 100,000. Indirect age adjustment was performed via regression of incidence on an age index and the mean arsenic level for each census tract. This was required since age data were lacking for many of the cases. The incidence of both cell types was less correlated with the age index (% $\geq$ 65 years) in males than in females. Multiple regressions on the age index and arsenic levels were not significantly different from regressions on the age index by itself, indicating that water arsenic levels were not related to skin cancer incidence in the county.

Fairbanks, Alaska

Harrington et al. (1978) studied exposure levels, absorption and possible health effects of arsenic in drinking water among residents of a 150-square-mile area near Fairbanks, Alaska. The discovery of high arsenic concentrations in the individual wells supplying homes in the area triggered the investigation. A control group consisting of households with well water arsenic concentrations below the EPA standard of 50 ug/L was selected from the same 150-square-mile area.

The arsenic body burden was assessed in urine, hair and nails. Both hair and urine levels showed a dose-response relationship with well water arsenic levels. Signs and symptoms of arsenic toxicity were evaluated from questionnaire and physical examination data.

Due to the fact that some individuals in the area routinely drank bottled water and that some well water drinkers switched to bottled water during the three months preceding the study, it was difficult to base exposures on well water concentrations and/or water consumption data alone. The 211 participants were divided into four exposure categories based on the type of water they drank: well water containing 100 ug/L or less, well water containing more than 100 ug/L, bottled water, or well water followed by a recent switch to bottled water. Total daily arsenic dose was determined for each

individual based on the number of glasses per day from each water source.

Results of the historical questionnaires, dermatological and peripheral neurological examinations are not provided in any detail in the report. The investigators stated that no differences were found in signs, symptoms or physical examination findings among any of the exposure categories. The lack of any skin cancer findings is not surprising, given the dose levels involved and the short ($\leq$10 years) duration of exposure for most subjects. The investigators also mention that low solar UV exposure, high socioeconomic status, good water quality and arsenic speciation may all be factors influencing the negative findings of their study.

West Millard County, Utah

Southwick et al. (1981) surveyed three communities in West Millard County, Utah, to test the hypothesis that "A population which consumes drinking water containing levels of arsenic which exceed National Drinking Water Standards by approximately four to eight times will show more signs and symptoms of chronic arsenic poisoning than a matched control population." Assessment of exposure to arsenic included: measurements of drinking water arsenic levels; water intake (including information on seasonal variations and detailed beverage intake obtained via questionnaire); work histories,

including arsenic exposure and environmental air monitoring for one year.

The wide range of values obtained for water consumption is somewhat surprising. Hinckley is the most extreme example with rates ranging from 0.3 to 13 L/day. Even taking the hot climate and agricultural work into account, 13 L/day seems rather high. No mention is made of any tests of the validity or reliability of the beverage intake questionnaires used. Such information would be of interest, since the average daily intakes reported are somewhat higher than the levels of "Daily Fluid Intake" which are described in the National Interim Drinking Water Regulations and commonly used to estimate doses received via intake of drinking water (USEPA 1977).

The evaluation of health effects involved an assessment of body burden, some laboratory evaluation and physical examination. Measurement of body burden included analysis of arsenic levels in urine and hair. With both measurements, a clear response effect was evident. In comparison with other studies in which urinary arsenic levels were obtained and compared to drinking water arsenic levels, the concentrations found in the Utah study are somewhat high. The investigators mentioned that the levels were probably inflated due to the laboratory's practice of reporting low values of urinary arsenic as less than 0.04 mg/L. For analysis, such values were treated as equal to 0.04 mg/L. No correction for specific grav-

ity was made in the analysis of urinary arsenic concentrations.

The physical examination included a health questionnaire, personal history questionnaire, hematocrit, neurological exam and dermatological exam. Of the eligible exposed participants, 65% went through a physical exam, and 46% of the eligible controls were examined.

Only 12 of the 249 participants were found to have any of the signs usually associated with arsenic toxicity. No tumors were found on body surfaces not exposed to solar UV radiation. Signs were found in 6.25% of the exposed participants examined and in 2.86% of the control participants. Regression analysis revealed no association between these signs and annual arsenic dose.

The age adjusted cancer rates for various communities in Millard County were obtained from a tumor registry and examined by Southwick et al. (1981) as part of their study. No breakdown by specific types of tumors was given in the report, and there was no statement indicating whether such detailed analysis was done. Hinckley was shown to have a lower overall cancer incidence than Delta. Death rates in the communities were also examined for the period 1956 to 1976. No particular patterns of cancer mortality were evident in Hinckley versus Delta. However, cancer mortality is a poor indicator for arsenical effects in terms of non-melanoma skin cancer due to the rela-

tively low rate of fatality from the disease.

There is some evidence that arsenic exposure may be associated with increased frequency of internal tumors. Several reports present data showing increased incidence of hemangioendothelial sarcoma (HAS) of the liver following arsenic exposure via Fowler's solution (Regelson et al. 1968, Lander et al. 1975), drinking water plus pica (Falk et al. 1981) or drinking water alone (Zaldivar et al. 1981).

An association between arsenic exposure and other types of internal tumors has been reported (Dobson et al. 1965, Graham and Helwig 1966, Sommers and McManus 1953, Reymann et al. 1978). However, many of these studies were poorly controlled and have not been subjected to statistical analysis. Thus, the significance of the findings are uncertain. For example, an association between basal cell carcinoma and internal malignancy has been noted in women treated with arsenic for verruca plana (Reymann et al. 1978), yet in the same study a lower-than-expected incidence was found in women treated for lichen planus. Individual variation in susceptibility, as well as difficulties in determining doses and the contribution of environmental arsenic sources to dose may be confounding factors (Reymann et al. 1978). Moreover, there are a number of studies which do not show a statistical relationship between arsenic and internal malignancy (Stolman and Garfinkel 1970, Bean et al. 1968). It is difficult to reach a conclusion on

this matter based on the available data.

The International Agency for Research on Cancer (IARC) has reviewed the evidence regarding the carcinogenic potential of arsenic, and has concluded that arsenic is a Group 1 compound (sufficient evidence for carcinogenicity in humans) (WHO 1982).

D. Quantification of Carcinogenic Effects

Only one study (that of Tseng et al. 1968) provides sufficient data to permit a quantitative assessment of cancer risk due to arsenic exposure. This analysis was described in USEPA (1980), and the results are shown in Table VIII-6. These values are very low compared to average arsenic exposure in apparently healthy populations, and the validity of the data and of the model have both been questioned. In an extensive evaluation of the available data, Andelman and Barnett (1983) concluded that while the model based on the Tseng et al. (1968) study was "reasonable", and was not invalidated by several negative findings in epidemiological studies in the U.S. (Goldsmith et al. 1972, Morton et al. 1976, Harrington et al. 1978, Southwick et al. 1981), nevertheless, due to a number of significant uncertainties "the Taiwan based prevalence model should not be used directly to predict the risk of arsenic-induced skin cancer in the United States".

Table VIII-6 Estimated Risk of Excess Cancer Due to Arsenic Ingestion

Risk level	As in water[a] (ng/L)
10^{-5}	22
10^{-6}	2.2
10^{-7}	0.22

[a]Assumes water consumption of 2 L/day, plus an average daily consumption of 6.5 g fish and shellfish.

Adapted from USEPA (1980).

Based on this analysis, it is judged that there is currently no suitable quantitative risk estimate for excess cancer due to arsenic ingestion which is applicable to the United States.

E. Existing Guidelines and Standards

The current MCL for arsenic is 50 ug/L (USEPA 1977). The derivation of this value involved consideration of the carcinogenic risk as well as the potential beneficial effects of arsenic. The calculation was based primarily on data showing an average consumption of 900 ug As/day in food (Schroeder and Balassa 1966), and the assumption that no more than 10% of total arsenic ingestion should be provided by drinking water. This value has been reconsidered periodically, but has not been changed. The conclusions and recommendations offered by NAS (1983) are as follows:

> "The epidemiological studies on U.S. populations have failed to confirm the association between arsenic in drinking water and the incidence of cancer observed in Taiwan. Furthermore, only 0.4% of the drinking water samples taken from public water supplies in the United States have exceeded a total arsenic concentration of 0.01 mg/liter (National Research Council, 1980). This finding is in sharp contrast to the 'average' concentration of 0.4 mg/liter (400 ppb)

reported in the Taiwan studies. It is therefore the opinion of this committee that 0.05 mg/liter provides a sufficient margin of safety, but that further experimental research and epidemiological evaluations of the association of elevated levels of arsenic in drinking water and skin cancer be undertaken."

In addition, NAS (1980, 1983) noted that:

"If 0.05 mg/kg of dietary [total] arsenic is also a nutritionally desirable level for people, then the adequate human diet should provide a daily intake of approximately 25 to 50 ug. The current American diet does not meet this presumed requirement."

F. Special Considerations

1. High-Risk Populations

Children are often more sensitive to toxicant exposure than adults, but no systematic study of arsenic toxicity as a function of age was located. Zaldivar (1974) reported that of the total number of patients diagnosed as having chronic arsenic poisoning in Antofagosta, Chile, 51% were children (0 to 10 years old). Zaldivar noted that this might be due to the higher water intake per unit body weight in children than adults, but also speculated that medical attention might be

sought more frequently for young children showing the signs of arsenic poisoning that for older children or adults with similar symptoms. Thus, whether children are truly more sensitive to arsenic than adults remains to be resolved.

Another group which may be more sensitive than the general population is persons with psoriasis. Arsenic was one of several treatments used to control psoriasis, and several investigators noted a higher-than-expected incidence of skin cancer in such patients (Neubauer 1947). However, psoriasis was also treated with other carcinogens (coal tar, UV radiation), and the relationship between arsenic exposure and skin cancer in psoriasis patients is presently unresolved.

2. Interactions

Mahaffey and Fowler (1977) studied interactive effects of lead, cadmium and arsenic in rats. Arsenic did not significantly alter the kidney or liver weights of rats over the separate actions of cadmium or lead. In fact, significant interactions were infrequent. A significant interaction was observed between arsenic and cadmium. Groups of 14 rats were administered arsenic (50 ppm) with lead (200 ppm) and/or cadmium (50 ppm). Arsenilic acid and sodium arsenate were used in the study. Animals were exposed for a 10-week period. Body weights were reduced by the combination with arsenic.

Food efficiency was reduced by arsenic and cadmium in combination. Red cell and other blood changes which were enhanced by arsenic were also seen.

Holmberg and Ferm (1969) found that selenium in the form of selinite provided some protection against arsenic-induced tertatology in the hamster. British anti-Lewisite (BAL) and 2,3-dimercaptopropanol reduced arsenic-induced malformations (Hood et al. 1977).

Obermeyer et al. (1971) reported that the toxicity of trimethylselenium chloride in rats was enhanced by concurrent administration of arsenite (the intraperitoneal LD_{50} declined from 49.4 mg/kg to about 3 mg/kg by dosing rats with 4 mg As/kg). The response in his chronic study suggested an increased toxicity of the selenium compound in the presence of arsenite. These findings are in contrast to the selenium and arsenic studies of Moxon and DuBois (1939), which showed that arsenic had a protective action against the liver damage induced in rats by selenium. These studies have been extended, and the evidence now suggests that the selenium-arsenic interaction has a metabolic basis.

3. Beneficial Effects

As discussed before, several studies in animals suggest that diets containing less than 50 to 100 ppb arsenic may be

sub-optimal for growth. It is not yet known whether this level of arsenic is beneficial in humans.

4. Other Factors

Numerous studies have found that arsenic toxicity is dependent upon the chemical state of the arsenical (As^{+3} > As^{+5}; inorganic > organic). In aerated water, especially chlorinated water, it would be expected that nearly all arsenic will be oxidized to the As^{+5} state, but As^{+3} may exist in water drawn from anaerobic sources.

F. Summary:

The recommended one-day and ten-day HA values for both adults and children and the AADI are summarized in Table VIII-7.

Table VIII-7 Summary of Quantification of Toxicological Effects

	Drinking water concentration (mg/L)		
	10-kg Child	70-kg Adult	References[a]
One-Day Health Advisory	0.14	1.0	Holland (1904)
Ten-Day Health Advisory			
AADI (100% from drinking water)	0.03	-[b]	Zaldivar (1974)

[a]References used in calculating HA or AADI values.

[b]Not calculated, because the child is more sensitive than the adult.

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